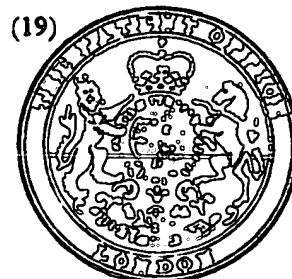


PATENT SPECIFICATION

(11) 1 458 514 ✓

1 458 514

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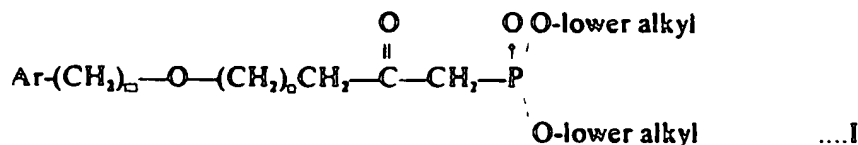


(54) SUBSTITUTED DIALKYL 2-OXOPROPYLPHOSPHONATES

(71) We, PFIZER INC, a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to intermediates useful in the preparation of certain novel analogs of the naturally occurring prostaglandins. In particular it relates to intermediates useful in the preparation of novel prostaglandins which are described and claimed in Patent Application 51758/73 (Serial No. 1,456,512).

The present invention provides a substituted dialkyl 2-oxopropyl phosphonate of the formula:

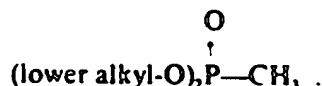


wherein Ar is phenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α - or β -naphthyl or mono-substituted phenyl wherein said substituent is halogen, trifluoromethyl, phenyl, lower alkyl or lower alkoxy; and n and m are each integers from 0 to 3 with the proviso that the sum of n and m does not exceed 3, and lower indicates a group of 1—6 carbon atoms.

The invention also provides a process for preparing a compound of the formula I, which comprises reacting a lower alkyl ester of the formula:



wherein Ar, m and n are as defined above, with a dialkyl methylphosphonate of the formula:



The starting materials for the various novel compounds of this invention are available commercially or are made by methods well known to those skilled in the art. For example, to make dimethyl 2-oxo-3-phenoxypropylphosphonate, the starting material for the synthesis of the 16-phenoxy-17,18,19,20-tetra-norprostaglandins, one cools a solution of dimethyl methylphosphonate in tetrahydrofuran to -78°C. in a dry nitrogen atmosphere and then adds *n*-butyl-lithium in hexane dropwise, slowly. After stirring methyl 2-phenoxyacetate is added dropwise. After 3 to 4 hours at -78°C. the reaction mixture is warmed to ambient temperature, neutralized with acetic acid and rotary evaporated to a white gel. The gelatinous material is taken up in water, the aqueous phase is extracted in

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$$\begin{array}{c} \text{O} \qquad \qquad \qquad \text{O} \\ | \qquad \qquad \qquad || \\ (\text{lower alkyl-O})_2\text{P}-\text{CH}_3 + \text{Ar}-(\text{CH}_2)_m-\text{O}-(\text{CH}_2)_n\text{CH}_2\text{C}-\text{O-lower alkyl} \\ | \qquad \qquad \qquad || \qquad \qquad \qquad | \\ \text{O} \qquad \qquad \text{O O-lower alkyl} \\ | \qquad \qquad | \\ \text{O-lower alkyl} \end{array}$$

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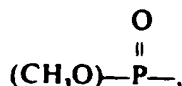
Dimethyl 2-Oxo-3-phenoxypropylphosphonate.

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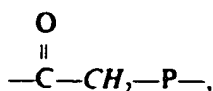
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-70° (20 minutes). After 3.5 hours at -78° the reaction mixture was allowed to warm to ambient temperature, neutralized with 14 ml. acetic acid and tary evaporated to a white gel. The gelatinous material was taken up in 175 ml. water, the aqueous phase extracted with 100 ml. portions of chloroform (3x), the combined organic extracts were backwashed (50 cc. H₂O), dried (MgSO₄), and concentrated (water aspirator) to a crude residue and distilled, b.p. 172—175° (0.5 mm) to give 24.6 g. dimethyl 2-oxo-3-phenoxypropylphosphonate.

The nmr spectrum (CDCl₃) showed a doublet centered at 3.75δ (J=11.5 cps, 6H) for



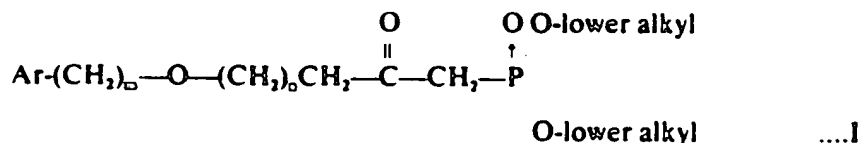
a singlet at 4.7δ (2H) for C₆H₅O—CH₂—CO—, a doublet centered at 3.24δ (J=23 cps, 2H)



and a multiplet at 6.8—7.5δ (5H) for the aromatic protons.

WHAT WE CLAIM IS:—

1. A compound of the formula:—



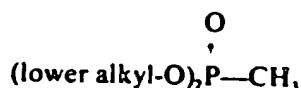
wherein Ar is phenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α- or β-naphthyl or monosubstituted phenyl wherein said substituent is halogen, trifluoromethyl, phenyl, lower alkyl or lower alkoxy; and n and m are each 0 or integers from 1 to 3 with the proviso that the sum of n and m does not exceed 3, and wherein "lower" indicates a group of 1—6 carbon atoms.

2. Dimethyl 2-oxo-3-phenoxypropylphosphonate.

3. A process for preparing a compound of formula I as claimed in claim 1, which comprises reacting a lower alkyl ester of the formula



wherein Ar, m and n are as defined in claim 1, with a dialkyl methylphosphonate of the formula:



4. A process for preparing a compound of formula I as claimed in claim 1, substantially as hereinbefore described with reference to the Example.

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